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LEPTOSPIROSIS COMPLICATIONS, CAUSES OF DEATH AND PATHOMORPHOGENESIS

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Abstract: Leptospirosis is a natural focal zoonosis that is widespread in the European territory of the Uzbekistan, characterized by a severe course and prolonged convalescence [1-3]. The disease is registered with different intensity in all districts of Russia (Figure 1), so in 2012 leptospirosis was observed in 37 administrative territories [4-6]. The highest incidence is observed in 2) [1, 7]. The active natural focus of leptospirosis in the Kuban region supports the incidence with periodic increases every 3-4 years (0.61–12.0 cases per 100 thousand populations). Since 2018, the incidence rate has decreased to 0.6-0.8 cases per 100 thousand populations, while sporadic cases with a severe complicated course with a mortality rate of up to 15% remain. Improved diagnosis and organization of medical care, and the introduction of new treatment regimens for leptospirosis significantly reduced mortality [8-12]. At the same time, the structure of fatal outcomes has changed, both in terms of the time of onset and the nature of the complications that determine them. Multiple organ failure syndrome and septic complications associated with the activation of endogenous infection or the addition of secondary complications against the background of immunodeficiency developing in severe leptospirosis began to come to the fore among life-threatening conditions [2, 13, and 14].

Keywords: leptospirosis, disease course, diagnosis, treatment, prevention.

Despite the ongoing scientific and practical developments, high mortality in leptospirosis demonstrates the unresolved issues of pathogenesis, therapy, and organization of care, in particular, the mechanisms of damage to the lungs, hemostasis, and kidneys, and the role of the systemic inflammatory response [15-19]. The modern concept of the body's response to damage in the form of systemic inflammatory response syndrome (SIRS) determines the accumulation and uncontrolled spread of aggressive pro-inflammatory mediators as the leading mechanisms of systemic damage [20, 21]. if in a localized process, mediators come from the primary inflammatory focus, then in CVD they are released by activated macrophages and other damaged cells in the "shock" organs and tissues. Manifestations of CVD in the form of shock followed by multiple organ dysfunctions, which turns into multiple organ failure, are the main causes of high mortality in sepsis in surgical and obstetric-gynecological practice [22]. The role of CVD in recent years has been considered in the pathogenesis of leptospirosis from the standpoint of both clinical and patho morphogenesis [13, 23, 25, 33]. Timely diagnosis of the disease and hospitalization to specialized medical centers play a significant role in the effectiveness of treatment of patients with leptospirosis [9, 26, 27]. The aim of this study was to improve the diagnosis and prognosis of the course of leptospirosis by studying the clinical features and patho morphogenesis, determining the leading causes of deaths at different stages of the disease, depending on the level of organization of specialized medical care. Materials and methods.

Leptospirosis is a natural focal zoonosis that is widespread in the European territory of the Russian Federation, characterized by a severe course and prolonged convalescence [1-3]. The disease is registered with different intensity in all districts of Uzbekistan, so in 2021 leptospirosis was observed in 37 administrative territories [4-6]. The highest incidence is observed in 2) [1, 7]. The active natural

focus of leptospirosis in the Kuban region supports the incidence with periodic increases every 3-4 years (0.61–12.0 cases per 100 thousand population). Since 2018, the incidence rate has decreased to 0.6-0.8 cases per 100 thousand population, while sporadic cases with a severe complicated course with a mortality rate of up to 15% remain. Improved diagnosis and organization of medical care, and the introduction of new treatment regimens for leptospirosis significantly reduced mortality [8-12]. At the same time, the structure of fatal outcomes has changed, both in terms of the time of onset and the nature of the complications that determine them. Multiple organ failure syndrome and septic complications associated with the activation of endogenous infection or the addition of secondary complications against the background of immunodeficiency developing in severe leptospirosis began to come to the fore among life-threatening conditions [2, 13, 14]. Despite the ongoing scientific and practical developments, high mortality in leptospirosis demonstrates the unresolved issues of pathogenesis, therapy, and organization of care, in particular, the mechanisms of damage to the lungs, hemostasis, and kidneys, and the role of the systemic inflammatory response [15-19]. Modern concept of the body's response to damage in the form of systemic 38hedral injury efferent detoxification methods (hemosorption, hemofiltration); Group 3-33 deaths in 1998-2008 – beginning of plasmapheresis and immune correctors; Group 4 – 18 deaths in 2009-2014-current stage. The autopsy material of 55 patients who died from leptospirosis during the period from 1986 to 2014 was studied. Autopsy samples were fixed in a 10% formalin solution and processed by the traditional method of manufacturing paraffin blocks, serial sections with a thickness of 5 microns, followed by staining with hematoxylin and eosin. The final diagnosis of leptospirosis was established on the basis of anamnesis, clinical and laboratory data, the results of pathologic and anatomical examination and staging of RMA with live leptospira cultures, ALS reaction, ELISA and PCR. the mortality rate in the region was 5.3%, and in patients with severe course-14.4%. The introduction of efferent detoxification methods and the development of protocols for their use in leptospirosis led to a decrease in mortality in 1989-1997 to 3.5%, and in severe cases - to 6.3%. The period 2008-2018 was characterized by an increase in morbidity in the region, while the use of plasmapheresis, immunocorrectors and improved organization of medical care allowed reducing its level to 2.9%, in severe cases - to 5.5%. In the period 2019-2024, the mortality rate in the region increased again to 8.5% in general and 15.8% in severe cases. During the considered periods, patients were admitted to the hospital for an average of 5.5±0.14 days of illness. The 6th-9th days of the disease were critical, accounting for 52% of all deaths. It should be noted the importance of starting therapy of the disease in the effectiveness of treatment. In the first 3 days of admission to the hospital, 63% of patients in groups 1-3 died, the average bed-day was 4.0±0.36 in group 1 and 1.4±0.15 in group 3. In recent years (Group 4), the percentage of deaths in the first 3 days of inpatient treatment decreased to 39, and the average bed day increased to 11.2±2.43. The average day of death from the onset of the disease in group 4 was 17.9±2.30 (Figure 3). The causes that determine the onset of death also changed accordingly. In the periods 1969-1988 and 1989-1997, the main causes of death were a combination of such complications as infectious and toxic shock (ITSH) – 53 and 57%, respectively, acute renal and hepatic insufficiency (OPN) – 40 and 44%, DIC-23 and 22%, acute respiratory distress syndrome (ARDS) – 32 4). In the first 5 days of leptospirosis, the main cause of death was ITSH, from day 6 to Day 10-acute renal failure, from the end of week 2 and later-acute liver failure (10%), edema and swelling of the brain (4, 6%), myocarditis (11, 14%). Later than the 11th day of the disease, the causes of death were OSF (9.9%). Thrombohemorrhagic syndrome (DIC-31%), gastrointestinal bleeding (13%), and brain hemorrhage (13%) are among the first to appear. The proportion of pneumonia (6%) and myocarditis (6%) decreased. Analysis of the causes of death of 18 patients with leptospirosis, which occurred in the period 2009-2014 (Group 4), revealed the following patterns. The rate of death from ITV in the first days of the disease decreased to 13%, OPN as the main cause of death was present in 25%, while the proportion of DIC-syndrome and ARDS increased to 50 and 44%, respectively (see Figure 4). Evaluation of the clinical picture in 125 patients with severe leptospirosis revealed a prognostic role in the development of the disease. significance of the frequency of registration of signs of CVD, evaluated according to the criteria adopted by the conciliatory conference of the societies of the American College of Thoracic Surgeons and the Society of Intensive Care Medicine.

[22]. The presence of two signs of CVD corresponded to a cyclical course of the disease with a favorable prognosis. The determination of three signs was observed with the development of various organ dysfunctions, but a favorable outcome of the disease. Registration of four signs of CVD served as a criterion for multiple organ failure and was noted in the group of patients with a fatal outcome.

Multiple organ dysfunction / insufficiency was recorded in all patients with severe leptospirosis, but its severity both in intensity and in the number of organs and systems involved varied significantly. With organ failure on the part of three organs and systems, the mortality rate was 9.8%, involvement of four organs and systems led to 71.4% mortality, five – to 97.9%, and more than five – determined 100% mortality. To dynamically assess the degree of dysfunction/ insufficiency of the leading systems in patients with leptospirosis with fatal outcomes treated in the ICU, we used the SofA organ dysfunction scale SofA, originally proposed for assessing multiple organ failure in patients with sepsis. The SofA scale is based on a point-based definition of dysfunction of six organ systems: respiratory, cardiovascular, hepatic, coagulation, urinary and central nervous systems from mild dysfunction (0 points) to severe insufficiency (4 points). The total assessment of the severity of the condition of patients is maximal at the 1st week of the disease and is 18.7±0.32 points. During this period, there were marked changes in the hemostatic system (4 points), cardiovascular system (3.4 points – ITSH grade III), respiratory system (3.1 points – ARDS), hepatic (3.9 points) and renal (3.2 points) insufficiency. In the dynamics of follow-up at 2-4 weeks, changes in the respiratory system decrease and more often correspond to acute lung damage (2.5-2.8 points), hemostatic lesions are 2.0–3.3 points, manifestations of liver failure persist (4.0–3.2 points). It should be noted that acute hepatic insufficiency, determined by the level of bilirubin, in leptospirosis is not a prognostic criterion in assessing the severity of the patient's condition, since high bilirubin values are recorded with the same frequency with favorable and unfavorable outcomes of the disease. The manifestations of acute renal failure gradually decrease with the transition from the anuria stage to the polyuria stage (3.2-2.4 points). On the part of the cardiovascular system, some stabilization occurs at week 2-3 (2.8–2.6 points), followed by decompensation at week 4-3.2 points. At week 5-6, the maximum manifestations of insufficiency are determined from the cardiovascular system (3.5 points) and the hemostatic system (3 points). Assessment of the severity of organ failure in patients with leptospirosis on the day of death on the SofA scale. Allowed us to compare the severity of final damage to organs and systems. Thus, 2 patients who died at the end of the 1st week of the disease (day 6, 5) had decompensated ITS (CVS-4 points) with the development of ARDS (3.5 points) and DIC (4 points) against the background of liver failure (4 points). Among the causes of death of 5 patients at week 2 (9.8±1.11 days), progressive renal failure was added to the complications listed above (4 points). Comparison with our previous studies [3, 10] shows that this group of patients with a severe course but a favorable outcome of the disease differs from the group of patients with a fatal outcome at the 1-2-th week of the disease by the lesion of the hemostatic system and respiratory organs (DIC + ARDS). In 6 cases, fatal outcomes occurred at the 4th-6th week of the disease. By this period of the disease, the signs of OPN were resolved to the level of 2 and 2.5 points. The course of leptospirosis was complicated by the development of pneumonia, sepsis, and septic shock, which became the main cause of death. Describing the fatal outcomes during 2009-2014 (Group 4), it should be noted that the patients were mostly residents of the region's districts (78%), men- 94%, the average age was 50.2±2.99 years, a characteristic epidemiological history was present in 72% of cases (professional-11%, fishing – 39%, swimming in water bodies-17%, contact with rodents-11%, contact with wet soil-11%). In recent years, the day of admission of patients to a specialized center (State Budgetary Institution "Specialized Clinical Infectious Diseases Hospital" of the Ministry of Health of the Krasnodar Territory, Regional Leptospirosis Center) has been extended to 7.8±0.98, while the initial request for medical care occurred on the 5.0±0.46 the day of illness. Initial therapy in 61% of cases was initiated in the conditions of the CRH. The percentage of comorbidities increased to 61% versus 32% in groups 2-3 and 19% in patients with a favorable outcome [13]. As an aggravating premorbid background of group 4 – newly identified neoplasms (retroperitoneal liposarcoma with invasion of the pancreas, clear cell adenoma of the left adrenal gland), liver cirrhosis of viral etiology B+D+C, chronic viral hepatitis C.

The established comorbidities included diseases of the cardiovascular system, chronic alcohol intoxication with multiple organ manifestations, and COPD. At patho-Anatablitsa 1 Dynamic assessment of the severity of organ failure in patients with leptospirosis treated in the ICU (according to the SOFA, Vincent scale J. etal., 1996; scores), M±m Organ system Indicator 1 week (n = 14) 2 weeks (n = 12) 3 weeks (n = 10) 4 weeks (n = 5) 5-6 weeks (n = 2) Respiratory Pao2 / FiO2 3,1±0,18 2,8±0,30 2,5±0,27 2,8±0,37 2,5±0,50 Hemostasis Platelets 4,0±0,00 3,3±0,36 2,4±0,60 2,0±0,89 3,0±1,00 Liver Bilirubin 3,9±0,10 4,0±0,00 3,7±0,21 3,2±0,20 2,5±0,50 CVS srAD 3,4±0,23 2,8±0,43 2,6±0,54 3,2±0,80 3,5±0,50 CNS Glasgow Scale 1,1±0,25 1,3±0,28 1,0±0,37 2,0±0,58 1,0±0,00 Kidneys Creatinine 3,2±0,30 3,2±0,37 2,8±0,36 2,4±0,81 2,0±1,00 Amount of points 18,7±0,32 17,3±1,06 15,0±1,34 16,0±2,63 14,5±0,50 Table 2 Assessment of the severity of organ failure in patients with leptospirosis on the day of death (on the SOFA scale, Vincent J. etal., 1996; scores), M±m Organ system Indicator 1 week (n = 2) 2 weeks (n = 5) 3 weeks (n = 5) 4 weeks (n = 4) 5-6 weeks (n = 2) Respiratory Pao2 / FiO2 3,5±0,50 3,0±0,58 2,6±0,40 2,8±0,48 2,5±0,50 Hemostasis Platelets 4,0±0,00 4,0±0,00 3,0±0,77 2,5±0,96 3,0±1,00 Liver Bilirubin 4,0±0,00 4,0±0,00 3,8±0,20 3,3±0,25 2,5±0,50 CVS srAD 4.0±0.00 3.8±0,25 3,0±0,77 4,0±0,00 3,5±0,50 Kidneys Creatinine 2,0±2,00 4,0±0,00 3,2±0,37 3,0±0,71 2,0±1,00 CNS Glasgow Scale 2,5±1,50 2,0±0,58 1,6±0,60 2,3±0,67 1,0±0,00 Amount of points 20,0±0,00 20,8±0,85 17,2±1,93 18,3±1,75 14,5±0,50 ragic transudate in the abdominal, pleural and pericardial cavities. Hemorrhages in the gastric mucosa – 18 (33%), epicardium and pericardium – 17 (31%), adrenal glands – 5 (9%), brain – 2 (4%), hemorrhagic pulmonary edema – 24 (44%) and gastrointestinal bleeding-8 (14.5%)were often detected in some cases. A characteristic feature was fullness of blood and swelling of internal organs (61%). Thus, an increase in blood filling of the vessels of the soft mater in the anatomical study of patients who died from leptospirosis in 51 (93%) cases macroscopically marked pronounced jaundice with ochre, reddish-yellow, saffron color, appearing against the background of a cyanotic general background and giving the organs a brown or clay tint. Hemorrhagic syndrome was typical, the signs of which in 13 (24%) patients were represented by hemorrhages in the skin, subcutaneous fat, mucous and serous membranes, in 19 (35%)-hemorrhoids

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